Generalized anxiety disorder (GAD) is a debilitating and chronic disorder affecting 6.8 million people in the United States in any given year (Anxiety and Depression Association of America, 2014). Although highly treatable, only about one-third of those suffering from anxiety-related disorders, such as GAD, receive treatment (Anxiety and Depression Association of America, 2014). Women are especially vulnerable to GAD, as they are twice as likely to develop the disorder (Anxiety and Depression Association of America, 2014). There are some significant barriers that may prevent women from receiving effective treatment for their anxiety (Shear, Cloitre, Pine, & Ross, 2005). Thus alternative approaches for GAD management focused exclusively on women need to be explored. Current research suggests that aspartame, a popular food additive used in many processed foods, may be involved in the pathogenesis of certain mental disorders (Humphries, Pretorius, & Naudé, 2008). It is hypothesized that high aspartame consumption will exacerbate GAD in women diagnosed with the condition.

Anxiety disorders in general are significantly more debilitating for women compared to men. Although both genders seem to follow a similar path in terms of the onset of anxiety disorders, women assume this path at a significantly greater rate. One study found that a diagnosis of an anxiety disorder, such as GAD, corresponded with more workplace absences for women, but not men (McLean, Asnaani, Litz, & Hofmann, 2011). Traditional gender roles may account for this disparity. Anxiety-related symptoms may go unrecognized in women due to gender-specific role expectations, which may normalize symptoms of worrying or fear. Women also tend to be the primary caregivers in their families, and this role may expose them to additional stressors that men may never encounter, further exacerbating their anxiety (Shear, Cloitre, Pine, & Ross, 2005). Hormonal changes caused by pregnancy, menstrual cycles, and birth control pills may also explain the prevalence of anxiety disorders in women (Calm Clinic, 2009). One study found that the synthetic hormones in birth control pills could potentially lead to alterations to the structure and function of women’s brains. Researchers examined the brains of 90 women, 44
of which took the birth control and 46 who experienced natural cycles. The lateral orbitofrontal cortex, which regulates emotions and reward response, was much thinner in women taking contraception. This alternation may be the cause of increased anxiety and depressive symptoms some women experience when taking oral contraception (Petersen, Troupoutoglou, Andreano, & Cahill, 2015). Anxiety may even pose a threat to unsuspecting women who have never been diagnosed with GAD or any other anxiety-related disorder. One longitudinal study assessed anxiety levels in middle-aged women over a 10-year period. Women who reported low anxiety at baseline were significantly more likely to meet the criteria for high anxiety symptoms during the perimenopausal (when a woman starts to have menstrual irregularities) and postmenopausal (absence of menstrual period for 12 consecutive months) stages of menopause. These results were independent of multiple risk factors, including upsetting life events, financial strain, fair/poor perceived health, and vasomotor symptoms (Bromberger, Kravitz, Chang, Randolph, Avis, Gold, & Matthews, 2013).

Individuals with anxiety disorders also use health care services more frequently than those who do not have an anxiety disorder (McLean et al., 2011), resulting in disproportionately high rates of medical health care service use (Wang et al., 2005). A huge portion of these health care service costs are directly related to the morbidity of anxiety disorders in women, as women have consistently higher prevalence rates of anxiety disorders compared to men (McLean et al., 2011). Another concern is the prevalence of those individuals with GAD that are receiving ineffective treatment or not seeking treatment at all. Typical approaches for managing GAD include pharmacotherapy or psychotherapy or a combination of two (Davidson, Feltner, & Dugar, 2010). However, of those individuals receiving treatment, including healthcare or other services, 42.5% are receiving treatment that is ‘minimally adequate’ (National Institute of Mental Health, 2014). This could be due to a combination of factors, such as the limited efficacy or adverse side effects from certain medications (Davidson et al., 2010). Additionally, GAD is often unrecognized or misdiagnosed due to a wide range of clinical presentations, including somatic symptoms or the presence of comorbid conditions (Weisberg, Dyck, Culppeper, & Keller, 2007). Further, the chronic and disabling nature of GAD may inhibit some individuals to fully respond to first-line treatment (Davidson et al., 2010). For some individuals with GAD, there is an overall reluctance towards getting the help they need. Many individuals cite a fear of diagnosis, social stigma, and treatment itself, as obstacles preventing them from seeking professional help (Tracy, 2012).

Many questions remain regarding the optimization of treatment for individual patients with GAD (Davidson et al., 2010). Many patients are exploring alternative remedies for the management and treatment of their psychological conditions. In recent years homeopathic herbal remedies have become increasingly popular (Lakhan & Vieira, 2010). In one study, chamomile supplements were found to benefit patients with GAD significantly more than those taking a placebo (Amsterdam, Li, Soeller, Rockwell, Mao, & Shults, 2009). Alternatively, in a double-blind randomized study, passionflower was shown to be equally as effective in treating GAD as a prescription anxiety medication (Akhoundzadeh, Naghavi, Vazirian, Shayegeanpour, Rashidi, & Khani, 2001).

Aside from individual nutritional supplements, diet quality is another approach that needs further exploration in the research of anxiety management. While various studies have examined the physiological consequences of a poor diet, more research is needed in investigating the relationship between dietary pattern and neurobehavioral functioning. Of particular concern are the food additives found in many of the highly processed foods consumed in the Western hemisphere. Aspartame, a common artificial sweetener used in processed foods, remains one of the most controversial food additives to date (Lindseth, Coolahan, Petros, & Lindseth, 2014). It has been suggested that high-aspartame consumption increases self-reports of irritability and depressive-like symptoms. One study examined the influence of aspartame consumption on cognition, depression, mood, and headache. Participants consumed high and low aspartame-containing meals for two weeks. Zung’s Self-Rating Depression Scale and Zung’s Irritability Scale were used to assess depression and mood. Upon completion of the high-aspartame diet, three out of the twenty-eight participants had a depression score over 49, which indicated mild to moderate clinical depression. Participants also reported higher irritability after consuming the high-aspartame diet compared to when they consumed the low-aspartame diet (Lindseth et al., 2014).

A study review also concluded that aspartame causes overall oxidative stress and neurodegeneration. Aspartame and its metabolites, aspartic acid and phenylalanine, cause nerves to fire excessively, indirectly causing a high rate of neuron depolarization. This leads to an inability for certain enzymes to function properly. Aspartic acid and phenylalanine may also be responsible for memory loss, as both components are neurotoxic without the other amino acids found in protein. Neurons of the brain may deteriorate, as these neurotoxic agents are able to cross the blood brain barrier. Aspartame also causes the endothelium of the capillaries to become more permeable, which leads to a compromised blood brain barrier (Humphries, Pretorius, & Naudé, 2008).

Simple dietary adjustments in combination with pharmacotherapy or psychotherapy may be useful for treating GAD patients. Although it has been suggested that following a holistic diet is beneficial for individuals suffering from anxiety (Hall-Flavin, 2014), few studies
have examined whether specific food additives enhance psychological stress in individuals with GAD. Additionally, few studies have focused exclusively on women with GAD and how diet may make the condition worse. Research on sex differences in anxiety is also lagging and little data exists regarding prevention, treatment, and public health policy efforts specifically aimed at women (Shear et al., 2005). Many studies have also been too reliant on self-report and clinical evaluations, as these assessment tools alone may be inaccurate. While there have been relatively few functional neuroimaging studies on GAD, there has been some support that GAD causes increased activation in the amygdala and medial prefrontal cortex (Shin, Davis, VanElzakker, Dahlgren, & Dubois, 2013). I am proposing a study that will examine the effects of aspartame consumption in women with GAD. I will utilize functional magnetic resonance imaging (fMRI) in addition to self-report and clinical assessments, to evaluate the chronicity of GAD. I am hypothesizing that consuming a diet high in aspartame will increase psychological stress levels for those participants with generalized anxiety disorder. Symptoms that coincide with generalized anxiety disorder will also be exacerbated.

**PROPOSED METHOD**

**Participants**

I plan to recruit 500 female participants between the ages of eighteen to forty five via the social media website Facebook. Ideally, a heterogeneous mix of participants would be preferred, representing all ethnic and racial backgrounds from different regions of the United States. I intend to recruit 250 participants diagnosed with GAD that are not medicated, and 250 not diagnosed with any mental disorder. All potential participants will be individually screened. The five DSM-5 criteria for GAD will be used to analyze if the disorder is present (see Appendix A). Those individuals who pass the screening will then be given a full description of the study, asked to fill out a consent form, and advised to undergo a physical health assessment to ensure that they are physically capable of undergoing dietary adjustments. Participants’ primary care doctors will also be contacted to verify that they are healthy candidates. If a conflict of interest ensues with a participant’s primary care doctor, those individuals will not be selected for study. A $500.00 (USD) incentive will be awarded upon completion of the study.

**Materials**

The materials that will be utilized in this study include prepared dietary meals, two stress assessments, Skype, an online video chat software, and functional magnetic resonance imaging (fMRI). The three meals and two snacks will contain either high doses of aspartame or no aspartame and will be prepared by a study dietitian. All of the dietary meals will be pre-measured and aspartame dosage will be calculated for each participant according to body weight. A previous calculation by Lindseth et al. (2014) will be used to determine a high dosage (25mg/kg x body weight) of aspartame for each participant. This calculation will be the allotted amount of aspartame each participant will intake daily. The meals and snacks will be portioned, prepackaged, and delivered to each participant’s residence before the study begins. A meal plan booklet will also be enclosed with the meals and snacks to instruct participants on what they must eat each day. The Center for Epidemiologic Studies (CES-D) scale will be used for participants’ self-reports of psychological stress (see Appendix B). The Hamilton Rating Scale for Depression (HRSD) will be used for the clinicians’ reports of psychological stress and will be conducted over Skype (see Appendix C). The fMRI will be used as a baseline comparison to assess any changes in amygdala and medial prefrontal cortex activation in each participant following each treatment condition.

**Procedure**

Participants will be randomly assigned to either the high-aspartame diet or the no-aspartame diet first for a period of two weeks (Phase 1). An initial fMRI will be performed before participants undergo both treatment sessions to use as a baseline. Participants will be required to document any changes in their mood or behavior throughout the study using daily journal logs, including the days that fall into a two-week washout period. They will be encouraged to write at least one page describing how they feel that day. Each participant will also be assigned to one of ten clinicians partaking in the study who will assess their psychological stress. Upon the 7th and the 14th day of Phase 1, participants will fill out the CES-D scale. They will then be advised to Skype their assigned clinicians who will ask them a series of questions listed on the HRSD scale. Another fMRI will be performed to assess the activation levels of each participant’s amygdala and medial prefrontal cortex. A two-week washout period will follow Phase 1 upon which participants are encouraged to follow their normal eating habits. After the washout period participants will switch to the other treatment condition (Phase 2). Upon the 7th and the 14th day of Phase 2, the CES-D scale and the HRSD scale will be completed in the same manner as in Phase 1. A final fMRI will be conducted as well.

**CONCLUDING REMARKS**

**Limitations**
The proposed study has a few limitations that are worth considering. This study is limited only to women between the ages of eighteen to forty five, and thus the potential findings will not be applicable to menopausal or postmenopausal women suffering from GAD. A second limitation is that diagnosis by clinicians may vary as every clinician differs slightly when assessing patients. Additionally, participants may not consume all of the dietary meals and snacks, thus compromising validity of the results. Another limitation is that participants may have a comorbid condition that has not been diagnosed, thus affecting the findings in this studies and compromising significance of results. A final limitation is that this study may be too demanding for some women, and thus there is a potential for a high dropout rate.

REFERENCES

ACKNOWLEDGEMENTS
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APPENDIX A

DSM-V Criteria for Generalized Anxiety Disorder

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).

B. The individual finds it difficult to control the worry.

C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months):

Note: Only one item is required in children.

1. Restlessness or feeling keyed up or on edge.
2. Being easily fatigued.
3. Difficulty concentrating or mind going blank.
4. Irritability.
5. Muscle tension.
6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).

D. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).

F. The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder, social phobia, contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).
## APPENDIX B

### The Center for Epidemiologic Studies (CES-D) Scale

Below is a list of some of the ways you may have felt or behaved. Please indicate how often you’ve felt this way during the past week. Respond to all items.

<table>
<thead>
<tr>
<th>Place a checkmark in the appropriate column.</th>
<th>Rarely or none of the time (less than 1 day)</th>
<th>Some or a little of the time (1-2 days)</th>
<th>Occasionally or a moderate amount of time (3-4 days)</th>
<th>All of the time (5-7 days)</th>
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<tr>
<td>During the past week...</td>
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<tr>
<td>1. I was bothered by things that usually do not bother me.</td>
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<td>2. I did not feel like eating; my appetite was poor.</td>
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<td>3. I felt that I could not shake off the blues even with help from my family.</td>
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<td>4. I felt that I was just as good as other people.</td>
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<td>5. I had trouble keeping my mind on what I was doing.</td>
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<td>6. I felt depressed.</td>
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<td>7. I felt that everything I did was an effort.</td>
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<td>8. I felt hopeful about the future.</td>
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<td>9. I thought my life had been a failure.</td>
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<td>10. I felt fearful.</td>
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<td>11. My sleep was restless.</td>
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<td>12. I was happy.</td>
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<td>13. I talked less than usual.</td>
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<td>15. People were unfriendly.</td>
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<td>16. I enjoyed life.</td>
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<td>17. I had crying spells.</td>
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<td>18. I felt sad.</td>
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<td>19. I felt that people disliked me.</td>
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<td>20. I could not “get going.”</td>
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APPENDIX C

Hamilton Rating Scale for Depression (HRSD)

To be administered by a health care professional. The higher the score, the more severe the depression.

1. DEPRESSED MOOD
   0=Absent
   1=These feeling states indicated only on questioning
   2=These feeling states spontaneously reported verbally
   3=Communicates feeling states non-verbally - i.e., through facial expression, posture, voice, and tendency to weep
   4=Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication

2. FEELINGS OF GUILT
   0=Absent
   1=Self reproach, feels he has let people down
   2=Ideas of guilt or rumination over past errors or sinful deeds
   3=Present illness is a punishment. Delusions of guilt
   4=Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. SUICIDE
   0=Absent
   1=Feels life is not worth living
   2=Wishes he were dead or any thoughts of possible death to self
   3=Suicidal ideas or gesture
   4=Attempts at suicide (any serious attempt rates 4)

4. INSOMNIA EARLY
   0=No difficulty falling asleep
   1=Complains of occasional difficulty falling asleep - i.e., more than ½ hour
   2=Complains of nightly difficulty falling asleep

5. INSOMNIA MIDDLE
   0=No difficulty
   1=Patient complains of being restless and disturbed during the night
   2=Waking during the night - any getting out of bed rates 2 (except for purposes of voiding)

6. INSOMNIA LATE
   0=No difficulty
   1=Waking in early hours of the morning but goes back to sleep
   2=Unable to fall asleep again if he gets out of bed

7. WORK AND ACTIVITIES
   0=No difficulty
   1=Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
   2=Loss of interest in activity; hobbies or work - either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
   3=Decrease in actual time spent in activities or decrease in productivity
   4=Stopped working because of present illness

8. RETARDATION: PSYCHOMOTOR (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)
   0=Normal speech and thought
   1=Slight retardation at interview
   2=Obvious retardation at interview
   3=Interview difficult
   4=Complete stupor

9. AGITATION
   0=None
   1=Fidgetiness
   2=Playing with hands, hair, etc.
   3=Moving about, can’t sit still
   4=Hand wringing, nail biting, hair-pulling, biting of lips

10. ANXIETY (PSYCHOLOGICAL)
    0=No difficulty
    1=Subjective tension and irritability
    2=Worrying about minor matters
    3=Apprehensive attitude apparent in face or speech
    4=Fears expressed without questioning

11. ANXIETY (SOMATIC): Physiological concomitants of anxiety, (i.e., effects of autonomic overactivity, “butterflies”, indigestion, stomach cramps, belching, diarrhea, palpitations, hyperventilation, paresthesia, sweating, flushing, tremor, headache, urinary frequency). Avoid asking about possible medication side effects (i.e., dry mouth, constipation)
    0=Absent
    1=Mild
    2=Moderate
    3=Severe
    4=Incapacitating

12. SOMATIC SYMPTOMS (GASTROINTESTINAL)
    0=None
    1=Loss of appetite but eating without encouragement from others. Food intake about normal
    2=Difficulty eating without urging from others. Marked reduction of appetite and food intake

13. SOMATIC SYMPTOMS GENERAL
    0=None
    1=Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability
2=Any clear cut symptom rates 2

14. GENITAL SYMPTOMS
0=Absent
1=Mild
2=Severe

15. HYPOCHONDRIASIS
0=Not present
1=Self-absorption (bodily)
2=Preoccupation with health
3=Frequent complaints, requests for help, etc.
4=Hypochondriacal delusions

16. LOSS OF WEIGHT (When rating by history)
0=No weight loss
1=Probably weight loss associated with present illness
2=Definite (according to patient) weight loss
3=Not assessed

17. INSIGHT
0=Acknowledges being depressed and ill
1=Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2=Denies being ill at all

18. DIURNAL VARIATION
A. Note whether symptoms are worse in morning or evening. If NO diurnal variation, mark none
0=No variation
1=Worse in A.M.
2=Worse in P.M.
B. When present, mark the severity of the variation. Mark “None” if NO variation
0= None
1=Mild
2=Severe

19. DEPERSONALIZATION AND DEREALIZATION
(Such as: feelings of unreality; Nihilistic ideas)
0=Absent
1=Mild
2=Moderate
3=Severe
4=Incapacitating

20. PARANOID SYMPTOMS
0=None
1=Suspicious
2=Ideas of reference
3=Delusions of reference and persecution

21. OBSESSIONAL AND COMPULSIVE SYMPTOMS
0=Absent
1=Mild
2=Severe

Total Score ________